treating each metabolic disease as a separate individual disease. At present, NSAID drugs alone cannot comprehensively inhibit many inflammatory factors and inflammatory pathways, and hypoglycemic drugs alone cannot fully restore glucose and lipid metabolism. For example, in order to obtain an adequate therapeutic effect in subjects with type 2 diabetes, fatty liver, polycystic ovary syndrome or obesity, it would be necessary to treat with a combination of drugs that jointly modulate inflammation and metabolism. This not only corrects impaired blood glucose and lipid homeostasis, but also alleviates clinically relevant metabolic comorbidities. More importantly, this can reduce the severity of diabetes-related complications. Therefore, subjects with metabolic syndrome should not be treated with only one drug, but should be treated with a combination of anti-inflammatory drugs and anti-metabolic disease drugs.

Summary ~~of the Invention~~

The object of the present ~~invention~~ disclosure is to overcome the deficiencies in the existing technologies, that is, the existing drugs on the market cannot effectively treat or prevent the metabolic syndrome caused by obesity, type 2 diabetes and insulin resistance. Thus, the present disclosure ~~invention~~ provides a pharmaceutical composition that not only corrects impaired glucose homeostasis, but also alleviates clinically relevant comorbidities, and more importantly, reduces the severity of diabetes-related complications.

In an aspect of the present disclosure, there is provided a pharmaceutical composition, comprising a therapeutic agent A and a therapeutic agent B, wherein the therapeutic agent A is a non-steroidal anti-inflammatory drug or a pharmaceutically acceptable salt thereof, and the therapeutic agent B is a fatty acid oxidation inhibitor or a pharmaceutically acceptable salt thereof.

In another aspect of the present disclosure, there is provided a use of a therapeutic agent A and a therapeutic agent B in the manufacture of a medicament for a combination therapy for treating one or more of overweight, obesity, visceral obesity, abdominal obesity, non-alcoholic fatty liver, non-alcoholic steatohepatitis, metabolic syndrome, a disease or condition that causes abnormal buildup of fat in the liver, atherosclerosis or complications thereof, glaucoma or complications thereof, polycystic ovary syndrome, dyslipidemia or complications thereof, and hyperlipidemia or complications thereof in a subject, wherein the therapeutic agent A is a non-steroidal anti-inflammatory drug or a pharmaceutically acceptable salt thereof, and the

therapeutic agent B is a fatty acid oxidation inhibitor or a pharmaceutically acceptable salt thereof.

In a further aspect of the present disclosure, there is provided a therapeutic agent A and a therapeutic agent B for use in therapy, wherein the therapeutic agent A is a non-steroidal anti-inflammatory drug or a pharmaceutically acceptable salt thereof, and the therapeutic agent B is a fatty acid oxidation inhibitor or a pharmaceutically acceptable salt thereof.

In order to achieve the object mentioned above, in one ~~aspect~~example, the present disclosure ~~invention~~ provides a pharmaceutical composition, which comprises a therapeutic agent A or a pharmaceutically acceptable salt thereof; a therapeutic agent B or a pharmaceutically acceptable salt thereof; and at least one pharmaceutically acceptable excipient, where the therapeutic agent A is a non-steroidal anti-inflammatory drug, and the therapeutic agent B is a fatty acid oxidation inhibitor.

In one ~~embodiment~~example, in the pharmaceutical composition, the therapeutic agent A and the therapeutic agent B are contained in a single dosage form.

In another ~~embodiment~~example, in the pharmaceutical composition, the therapeutic agent A and the therapeutic agent B are present in separate dosage forms.

In one ~~embodiment~~example, the therapeutic agent A is at least one selected from a salicylate, ibuprofen, indomethacin, flurbiprofen, phenoxyibuprofen, naproxen, nabumetone, piroxicam, phenylbutazone, diclofenac, fenprofen, ketoprofen, ketorolac, tetraclofenamic acid, sulindac, and

tolmetin.

In another ~~embodiment~~example, the therapeutic agent B is selected from trimetazidine, etomoxir, aminocarnitine or a phosphonooxy derivative of carnitine.

In some ~~embodiment~~examples, the present disclosure ~~invention~~ provides a pharmaceutical composition, which comprises a therapeutic agent A or a pharmaceutically acceptable salt thereof; a therapeutic agent B or a pharmaceutically acceptable salt thereof; and at least one pharmaceutically acceptable excipient, where the therapeutic agent A is a salicylate, and the therapeutic agent B is trimetazidine.

In some ~~embodiment~~examples, the present disclosure ~~invention~~ provides a pharmaceutical composition, which comprises a therapeutic agent A or a pharmaceutically acceptable salt thereof; a therapeutic agent B or a pharmaceutically acceptable salt thereof; and at least one pharmaceutically acceptable excipient, where the therapeutic agent A is aspirin, and the therapeutic agent B is trimetazidine.

In some ~~embodiment~~examples, the therapeutic agent A (e.g., a salicylate, such as aspirin) and the therapeutic agent B (e.g., trimetazidine) are in a weight ratio of 1:1 to 10:1, including 2:1 , 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, or 10:1. In some ~~embodiment~~examples, the weight ratio of the therapeutic agent A (e.g., a salicylate, such as aspirin) to the therapeutic agent B (e.g., trimetazidine) is 6:1.

In some ~~embodiment~~examples, the pharmaceutical dosage form thereof is an oral dosage form. In some ~~embodiment~~examples, the pharmaceutical dosage form is an injectable dosage form.

In another ~~aspect~~example, the present disclosure ~~invention~~ further provides the use (or method) of the therapeutic agent A and the therapeutic agent B in the preparation of a medicament for treating type 1 diabetes, type 2 diabetes, impaired glucose tolerance, impaired fasting glucose, hyperglycemia, postprandial hyperglycemia, overweight, obesity and metabolic syndrome; or improving glycemic control and/or reduce fasting plasma glucose, postprandial plasma glucose and/or HbA1c; or slowing, delaying or reversing the progression from impaired glucose tolerance, impaired fasting glucose, insulin resistance and/or metabolic syndrome to type 2 diabetes; or treating diabetic complications such as cataracts, as well as microvascular and macrovascular diseases such as nephropathy, retinopathy, neuropathy, tissue ischemia, arteriosclerosis, myocardial infarction, stroke and peripheral arterial occlusive disease; or losing weight or promoting weight loss; or treating pancreatic β-cell degeneration and/or decreased pancreatic β-cell function, and/or restoring pancreatic β-cell function, and/or restoring pancreatic

insulin secretion; or treating a disease or condition that causes abnormal buildup of fat in the liver; or maintaining and/or improving insulin sensitivity and/or treating hyperinsulinemia and/or insulin resistance; or treating atherosclerosis and complications of atherosclerosis; or treating glaucoma and glaucoma complications; or treating dyslipidemia/hyperlipidemia and complications of dyslipidemia/hyperlipidemia, or treating reproductive-related metabolic diseases in a subject in need thereof, or a treatment method thereof, in which the therapeutic agent A is a non-steroidal anti-inflammatory drug, and the therapeutic agent B is a fatty acid oxidation inhibitor.

In one ~~embodiment~~example, the subject is an individual who is diagnosed with one or more conditions selected from overweight, obesity, visceral obesity, and abdominal obesity.

In another ~~embodiment~~example, the subject is an individual who is diagnosed with one or more of the following conditions:

(a) a fasting blood glucose or serum glucose concentration is greater than 110 mg/dL, especially greater than 125 mg/dL;

(b) a postprandial plasma glucose concentration is equal to or greater than 140 mg/dL; and

(c) an HbA1c value is equal to or greater than 6.5%, especially equal to or greater than 8.0%.

In another ~~embodiment~~example, the subject is an individual with one or more of the following conditions:

(a) obesity, visceral obesity and/or abdominal obesity;

(b) a triglyceride blood concentration ≥ 150mg/dL;

(c) an HDL-cholesterol blood level < 40 mg/dL in a female subject, or an HDL-cholesterol blood level < 50mg/dL in a male subject;

(d) systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg;

(e) a fasting blood glucose level ≥ 110 mg/dL; and

(f) an LDL-cholesterol blood level ≥ 130 mg/dL.

In another ~~embodiment~~example, the subject is an individual who is contraindicated in metformin monotherapy and/or intolerant to therapeutic doses of metformin.

In another ~~embodiment~~example, the subject is an individual with insufficient glycemic control after the treatment with one or more antidiabetic drugs selected from the group consisting of:

(a) a biguanide;

(b) a sulfonylurea;

(c) a meglitinide;

(d) a thiazolidinedione;

(e) an α-glucosidase inhibitor;

(f) insulin and an insulin analog;

(g) a dipeptidyl peptidase IV inhibitor;

(h) an SGLT2 inhibitor;

(i) a PPARα modulator;

(j) a glucose-dependent insulinotropic polypeptide agonist;

(k) a β-3 agonists;

(l) GLP1 and a GLP1 analog;

(m) a PPARγ modulator; and

(n) an HMG-CoA reductase inhibitor.

The pharmaceutical composition according to the present disclosure ~~invention~~ shows very good efficacy in glycemic control, especially in the reduction of fasting plasma glucose, postprandial plasma glucose and/or glycosylated hemoglobin (HbA1c); at the same time, it can effectively treat or prevent metabolic syndrome diseases caused by obesity, non-alcoholic fatty liver disease, polycystic ovary syndrome, type 2 diabetes and insulin resistance.

In some ~~embodiment~~examples, the therapeutic agent A is selected from a salicylate and the therapeutic agent B is selected from trimetazidine.

In some ~~embodiment~~examples, the therapeutic agent A is selected from aspirin and the therapeutic agent B is selected from trimetazidine.

In some ~~embodiment~~examples, the therapeutic agent A (e.g., a salicylate, such as aspirin) and the therapeutic agent B (e.g., trimetazidine) are in a weight ratio of 1:1 to 10:1, including 2:1 , 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, or 10:1. In some ~~embodiment~~examples, the weight ratio of the therapeutic agent A (e.g., a salicylate, such as aspirin) to the therapeutic agent B (e.g., trimetazidine) is 6:1.

In some ~~embodiment~~examples, the therapeutic agent A and the therapeutic agent B are administered simultaneously. In some ~~embodiment~~examples, the therapeutic agent A and the therapeutic agent B are contained in a single dosage form. In some ~~embodiment~~examples, the single pharmaceutical dosage form is an oral dosage form.

In some ~~embodiment~~examples, the therapeutic agent A and the therapeutic agent B are administered separately. In some ~~embodiment~~examples, the therapeutic agent A is administered before the therapeutic agent B. In some ~~embodiment~~examples, the therapeutic agent A is administered after the therapeutic agent B. In some ~~embodiment~~examples, therapeutic agent A and therapeutic agent B are administered orally, respectively. In some ~~embodiment~~examples, therapeutic agent A and therapeutic agent B are administered separately by injection.

Other features and advantages of the present disclosure ~~invention~~ will be described in detail in the following description of specific ~~embodiment~~examples.

Brief Description of the Drawings

The accompanying drawings are provided to facilitate further understanding of the present invention and constitute a part of this specification; the drawings are used to explain the present invention along with the following specific embodiments, but do not constitute a limitation of the present invention. In the drawings:

Fig. 1 shows the results of weight changes in diet-induced obesity (DIO) mice after 10 days of treating with the pharmaceutical therapeutic agents A+B in an experimental group using a pharmaceutical composition according to an embodiment of the present invention, as compared with the control group(s).

Fig. 2 shows the results of fat reduction in DIO mice induced by treating with the pharmaceutical therapeutic agents A+B in an experimental group using a pharmaceutical composition according to an embodiment of the present invention, as compared with the control group(s).

Fig. 3 shows the results of the morphology of adipocytes in the gonadal fat pad in an experimental group treated with the pharmaceutical composition according to an embodiment of the present invention, as compared with a DIO control group(s).

Fig. 4 shows the results of fatty liver and liver cell morphology in an experimental group treated with the pharmaceutical composition according to an embodiment of the present invention, as compared with a DIO control group(s).

Fig. 5 shows the results of cardiac muscle cell morphology in an experimental group treated with the pharmaceutical composition according to an embodiment of the present invention, as compared with a DIO control group(s).

Claims

1. A pharmaceutical composition, comprising a therapeutic agent A and~~or a pharmaceutically acceptable salt thereof;~~ a therapeutic agent B ~~or a pharmaceutically acceptable salt thereof; and at least one pharmaceutically acceptable excipient~~, wherein the therapeutic agent A is a non-steroidal anti-inflammatory drug or a pharmaceutically acceptable salt thereof, and the therapeutic agent B is a fatty acid oxidation inhibitor or a pharmaceutically acceptable salt thereof.

2. The pharmaceutical composition according to claim 1, wherein in the pharmaceutical composition, the therapeutic agent A and the therapeutic agent B are contained in a single dosage form.

3. The pharmaceutical composition according to claim 1, wherein in the pharmaceutical composition, the therapeutic agent A and the therapeutic agent B are present in separate dosage forms.

4. The pharmaceutical composition according to any one of claims 1~~ to~~ 3,
i) wherein the therapeutic agent A is ~~at least~~ one or more selected from the group consisting of a salicylate, ibuprofen, indomethacin, flurbiprofen, phenoxyibuprofen, naproxen, nabumetone, piroxicam, phenylbutazone, diclofenac, fenprofen, ketoprofen, ketorolac, tetraclofenamic acid, sulindac, tolmetin, and a pharmaceutically acceptable salt thereof; and/or ~~and tolmetin.~~

ii) wherein the therapeutic agent B is selected from the group consisting of trimetazidine, etomoxir, aminocarnitine, a phosphonooxy derivative of carnitine, and a pharmaceutically acceptable salt thereof.

~~5. The pharmaceutical composition according to claims 1 to 4, wherein the therapeutic agent B is selected from trimetazidine, etomoxir, aminocarnitine or a phosphonooxy derivative of carnitine.~~

~~6~~5. The pharmaceutical composition according to any one of claims 1~~ 4 to 5~~, wherein the

therapeutic agent A is ~~selected as~~ a salicylate or a pharmaceutically acceptable salt thereof, and the therapeutic agent B is ~~selected as~~ trimetazidine or a pharmaceutically acceptable salt thereof.

~~7~~6. The pharmaceutical composition according to any one of claims 1-5 ~~to 6~~, wherein the therapeutic agent A is ~~selected as~~ aspirin or a pharmaceutically acceptable salt thereof ~~(acetylsalicylic acid)~~.

~~8~~7. The pharmaceutical composition according to any one of claims 1-6 ~~to 7~~,

i) wherein a weight ratio of the therapeutic agent A to the therapeutic agent B is from 1:1 to 10:1, ~~and preferably~~optionally 6:1; and/or

ii) wherein the therapeutic agent A is at a dose of between 0.3 mg/kg and 120 mg/kg body weight, and the therapeutic agent B is at a dose of between 0.05 mg/kg and 500 mg/kg body weight.

8. The pharmaceutical composition according to any one of claims 1-7, which is for oral administration or injection.

9. Use~~A use~~ of a therapeutic agent A and a therapeutic agent B in the manufacture~~preparation~~ of a medicament for a combination therapy for treating one or more of overweight, obesity, visceral obesity, abdominal obesity, non-alcoholic fatty liver, non-alcoholic steatohepatitis, ~~and~~ metabolic syndrome,~~; or treating~~ a disease or condition that causes abnormal buildup of fat in the liver,~~; or treating~~ atherosclerosis or~~and~~ complications thereof,~~of atherosclerosis; or treating~~ glaucoma or~~and~~ complications thereof, polycystic ovary syndrome,~~of glaucoma; or treating~~ dyslipidemia or complications thereof, and ~~/~~hyperlipidemia or~~and~~ complications thereof~~of dyslipidemia/hyperlipidemia~~ in a subject ~~in need thereof~~, wherein the therapeutic agent A is a non-steroidal anti-inflammatory drug or a pharmaceutically acceptable salt thereof, and the therapeutic agent B is a fatty acid oxidation inhibitor or a pharmaceutically acceptable salt thereof.

10. ~~The use according to claim 9, wherein the subject is an individual who is diagnosed with one or more conditions selected from the group consisting of overweight, obesity, visceral~~

~~obesity, and abdominal obesity~~ The use of claim 9, wherein the subject is diagnosed with one or more of the following conditions:

(a) a fasting blood glucose or serum glucose concentration of greater than 110 mg/dL;

(b) a postprandial plasma glucose concentration of equal to or greater than 140 mg/dL;

(c) an HbA1c value of equal to or greater than 6.5%, optionally equal to or greater than 8.0%;

(d) obesity, visceral obesity, and/or abdominal obesity;

(e) a triglyceride blood concentration of equal to or greater than 150mg/dL;

(f) an HDL-cholesterol blood concentration of less than 40mg/dL in a female subject or an HDL-cholesterol blood concentration of less than 50mg/dL in a male subject;

(g) systolic blood pressure of equal to or greater than 130mmHg, and diastolic blood pressure of equal to or greater than 85mmHg;

(h) an LDL-cholesterol blood concentration of equal to or greater than 130 mg/dL.

11. The use ~~according to~~of claim 9 or 10,

(i) wherein the subject is contraindicated in metformin monotherapy and/or intolerant to a therapeutic dose of metformin; and/or

(ii) wherein the subject is an individual with insufficient glycemic control after treatment with one or more antidiabetic drugs selected from the group consisting of:

(a) a biguanide;

(b) a sulfonylurea;

(c) a meglitinide;

(d) a thiazolidinedione;

(e) an alpha-glucosidase inhibitor;

(f) insulin and insulin analog;

(g) a dipeptidyl peptidase IV inhibitor;

(h) an SGLT2 inhibitor;

(i) a PPARα modulator;

(j) a glucose-dependent insulinotropic polypeptide agonist;

(k) a beta-3 agonist;

(l) GLP1 and GLP1 analog;

(m) a PPARγ modulator; and

(n) an HMG-CoA reductase inhibitor~~wherein the therapeutic agent A is selected as aspirin~~.

12. The use of any one of claims 9-11, wherein the subject is a human.

13. The use of any one of claims 9-12,

i) wherein the therapeutic agent A is one or more of a salicylate, ibuprofen, indomethacin, flurbiprofen, phenoxyibuprofen, naproxen, nabumetone, piroxicam, phenylbutazone, diclofenac, fenprofen, ketoprofen, ketorolac, tetraclofenamic acid, sulindac, tolmetin, and a pharmaceutically acceptable salt thereof; and/or

ii) wherein the therapeutic agent B is selected from the group consisting of trimetazidine, etomoxir, aminocarnitine, a phosphonooxy derivative of carnitine, and a pharmaceutically acceptable salt thereof.

14. The use of any one of claims 9-13,

i) wherein the therapeutic agent A is a salicylate or a pharmaceutically acceptable salt thereof; and/or

ii) wherein the therapeutic agent B is trimetazidine or a pharmaceutically acceptable salt thereof.

15. The use of any one of claims 9-14, wherein the therapeutic agent A is aspirin or a pharmaceutically acceptable salt thereof.

~~12~~16. The use of~~according to~~ any one of claims 9-15~~ to 11~~,

i) wherein a weight ratio of the therapeutic agent A to the therapeutic agent B is from 1:1 to 10:1, optionally~~and preferably~~ 6:1; and/or

ii) wherein the therapeutic agent A is at a dose of between 0.3 mg/kg and 120 mg/kg body weight, and the therapeutic agent B is at a dose of between 0.05 mg/kg and 500 mg/kg body weight.

~~13~~17. The use according to any one of claims 9-16 ~~to 12~~, wherein the medicament comprising the therapeutic agent A and the therapeutic agent B is for simultaneous administration, optionally wherein the medicament comprising the therapeutic agent A and the therapeutic agent B is contained in a single dosage form~~are administered simultaneously~~.

~~14. The use according to claim 13, wherein the therapeutic agent A and the therapeutic agent B are contained in a single dosage form.~~

~~15~~18. The use according to any one of claims 9-16 ~~to 12~~, wherein the medicament comprising the therapeutic agent A and the therapeutic agent B is for sequential administration ~~are administered separately~~.

~~16~~19. The use according to claim ~~15~~18,

i) wherein the therapeutic agent A is ~~administered~~ for administration before the therapeutic agent B is to be administered; or

ii) wherein the therapeutic agent A is for administration after the therapeutic agent B is to be administered.

~~17. The use according to claim 15, wherein the therapeutic agent A is administered after the therapeutic agent B.~~

~~18~~20. The use according to any one of claims 9-19 ~~to 17~~, wherein the medicament is for oral or injection administration~~therapeutic agent A and the therapeutic agent B are administered orally or by injection~~.

21. The use according of any one of claims 9-20, wherein the medicament is to be administered, and wherein the administration of the medicament has one or more effects selected from the group consisting of:

(i) restoring skeletal muscle insulin sensitivity, restoring protein anabolism, restoring mitochondrial metabolism, alleviating muscle inflammation, alleviating muscle fibrosis, alleviating insulin resistance, alleviating sarcopenia syndrome, alleviating metabolic syndrome,

reversing insulin resistance, reducing serum total protein, reducing serum creatinine, reducing serum lactate dehydrogenase (LDH), reducing creatine kinase (CK), reducing cardiac creatine kinase isoenzyme MB (CKMB), and/or reducing α-hydroxybutyrate dehydrogenase (HBDH), wherein the subject is diagnosed with polycystic ovary syndrome;

(ii) ameliorating or reversing cardiovascular diseases such as myocardial fibrosis, ventricular hypertrophy, and/or heart failure, wherein the subject is diagnosed with polycystic ovary syndrome or non-alcoholic steatohepatitis;

(iii) curbing weight gain, reversing hyperlipidemia, reducing fasting blood glucose, reducing serum aspartate aminotransferase (AST), reducing triglyceride blood concentration, reducing total cholesterol, reducing LDL-cholesterol, and/or reducing HDL-cholesterol, wherein the subject is diagnosed with polycystic ovary syndrome or non-alcoholic steatohepatitis;

(iv) reversing liver enlargement, reversing liver damage, reducing the number of liver fat granules, reducing the size of liver fat granules, and/or reducing liver inflammatory cells, wherein the subject is diagnosed with non-alcoholic steatohepatitis;

(v) increasing glucose tolerance, reducing serum fasting insulin, promoting glucose and lipid metabolism, inhibiting inflammation, reversing insulin resistance, restoring skeletal muscle sensitivity, restoring liver insulin sensitivity, and/or relieving muscle inflammation, wherein the subject is diagnosed with non-alcoholic steatohepatitis;

(vi) promoting angiogenesis and/or neuromuscular tissue sensitivity, wherein the subject is diagnosed with non-alcoholic steatohepatitis;

(vii) modulating p38 and AMPK signaling pathways;

(viii) reducing body weight;

(ix) reducing the content of body fat;

(x) causing no cardiotoxicity;

(xi) causing no muscle toxicity and/or muscle loss;

(xii) causing no renal toxicity;

(xiii) reducing total serum cholesterol, serum LDL-cholesterol, serum alanine aminotransferase (ALT), and/or albumin/globulin ratio;

(xiv) causing no reduction in serum total protein;

(xv) increasing glucose tolerance, increasing insulin sensitivity, and/or reversing cell senescence;

(xvi) recovering a normal estrous cycle and/or increasing follicle-stimulating hormone (FSH), wherein the subject is diagnosed with polycystic ovary syndrome;

(xvii) after short-term administration, promoting the p38 and AMPK signaling pathways and the downstream targets, promoting catabolism such as fat hydrolysis and fatty acid oxidation; and

(xviii) after long-term administration, inhibiting the p38 and AMPK signaling pathways and the downstream targets, promoting anabolism, and/or promoting muscle repair.

22. A therapeutic agent A and a therapeutic agent B for use in therapy, wherein the therapeutic agent A is a non-steroidal anti-inflammatory drug or a pharmaceutically acceptable salt thereof, and the therapeutic agent B is a fatty acid oxidation inhibitor or a pharmaceutically acceptable salt thereof.